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ASSIMILATION AND HEREDITY.

I.

THE PROBLEM of the transformation of dead matter into living matter is continually being solved by each living cell. The most striking example of this process is the bird's egg, in which during the incubation a small piece of living matter, the germ, gradually transforms the whole yolk into living matter. It is just as evident in a growing organism. The transformation of the dead matter of the food into the living protoplasm of the body causes the growth of the child. We call this process of transformation of dead matter into living matter assimilation. Should we ever attempt to produce living matter artificially, this could only be done upon the basis of a careful analysis of assimilation.

The proteids and probably all constituents of living matter are generally different in the different species. Even the layman can recognise this through his chemical senses (taste and smell). The meat of the chicken and beef has a different flavor and odor, the various kinds of game taste and smell differently, etc. It is one of the fundamental facts of assimilation that the cells of an animal transform the proteids of another animal into their own protoplasm. If we feed a young dog during its period of growth with horse meat, thė horse meat will be transformed into dog's meat, and in this form it will be deposited. How does this process of transformation take place?

The proteids have a very large molecule. The formula of constitution for the proteid contained in the hemoglobin of the horse is $C_{680}H_{1098}N_{210}S_2O_{241}$, that of the hemoglobin of the dog is $C_{726}H_{1171}N_{194}S_3O_{214}$. The transformation of the former into the latter is only possible if two molecules of horse hemoglobin are split up into smaller building stones from which, by a new way of grouping, a molecule of hemoglobin of a dog is built up. Hence we see that the process of assimilation takes place in two phases, first a phase of cleavage and second a phase of synthesis of the small building stones into a new giant molecule.

But the cleavages and synthetical processes must be different in the protoplasm of different animals. The cells of a cat, for instance, split and put together the proteid molecules of horse meat in a different way from the cells of the dog. How does living matter split up the complicated molecules of our food, and why does this happen in a manner which is characteristic of and different for each species?

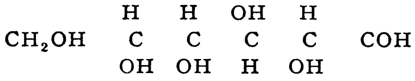
We know that the cleavage of the large molecules of our food into smaller molecules is brought about by ferments. The majority of investigators assume that a ferment is a special well defined molecule, but this is by no means certain, as we have not yet succeeded in finding out the chemical constitution of any ferment. To know whether the ferments of the living animal or living plant are something which we may hope to produce artificially in our laboratory, or whether they can only be found in living matter, is one of the fundamental problems of physiology. The possibility of producing living matter artificially and of producing new animal and plant forms depends to some extent upon our success in obtaining a more definite knowledge of the character of ferments.

II.

One of the most important steps in our knowledge of the mechanics of fermentation is connected with the work of Emil Fischer on sugars. It has been known for a long time that a molecule of grape sugar is split up by yeast (for instance, Saccharomyces cerevisiæ) into two molecules of alcohol and two molecules of carbonic acid. Fischer succeeded in discovering a series of sugars which do not like grape sugar contain six atoms of carbon in the molecule, but three, four, five, seven, eight, and nine atoms of carbon. The names of these sugars are triose, tetrose, pentose, etc., to nonose. It was found that Saccharomyces cerevisiæ is able to ferment only those sugars which contain three, six, or nine atoms of carbon in the molecule, while the other sugars are not fermentable. Thus the fermentability is a function of the number of the atoms of carbon in the molecule.

But a much more important relation exists if we consider not only the constitution of the sugar molecule but also its configuration. The molecule of grape sugar has the constitution $C_6 H_{12} O_6$. According to the various configurations of the atoms in this molecule, sixteen isomeric sugar molecules with the constitution $C_6 H_{12} O_6$ (Hexaldoses) are possible, a number of which are known. By means of a number of investigations it has been established that only three of these hexoses are fermentable with Saccharomyces cerevisiae, namely, d-glucose, d-mannose, d-galactose. This dependence of fermentability upon the configuration of the molecule becomes more evident if we compare some of the formulæ of the hexoses which are fermentable with those which are not fermentable.

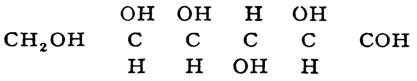
1. d-Glucose



$$CH_2OH \quad \underset{OH}{\overset{H}{C}} \quad \underset{OH}{\overset{H}{C}} \quad \underset{H}{\overset{OH}{C}} \quad \underset{OH}{\overset{H}{C}} \quad COH$$

(Fermentable.)

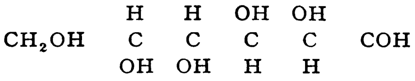
2. l-Glucose



$$CH_2OH \quad \underset{H}{\overset{OH}{C}} \quad \underset{H}{\overset{OH}{C}} \quad \underset{OH}{\overset{H}{C}} \quad \underset{H}{\overset{OH}{C}} \quad COH$$

(Non-fermentable.)

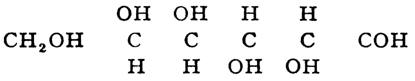
3. d-Mannose



$$CH_2OH \quad \underset{OH}{\overset{H}{C}} \quad \underset{OH}{\overset{H}{C}} \quad \underset{H}{\overset{OH}{C}} \quad \underset{H}{\overset{OH}{C}} \quad COH$$

(Fermentable.)

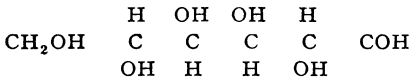
4. l-Mannose



$$CH_2OH \quad \underset{H}{\overset{OH}{C}} \quad \underset{H}{\overset{OH}{C}} \quad \underset{OH}{\overset{H}{C}} \quad \underset{OH}{\overset{H}{C}} \quad COH$$

(Non-fermentable.)

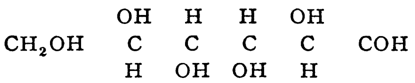
5. d-Galactose



$$CH_2OH \quad \underset{OH}{\overset{H}{C}} \quad \underset{H}{\overset{OH}{C}} \quad \underset{H}{\overset{OH}{C}} \quad \underset{OH}{\overset{H}{C}} \quad COH$$

(Fermentable.)

6. l-Galactose



$$CH_2OH \quad \underset{H}{\overset{OH}{C}} \quad \underset{OH}{\overset{H}{C}} \quad \underset{OH}{\overset{H}{C}} \quad \underset{H}{\overset{OH}{C}} \quad COH$$

(Non-fermentable.)

If we ask what is common to the sugars which are fermentable we see that it is their close relationship to d-glucose. It is only necessary to exchange an H-O and an H-group in order to transform d-galactose and d-mannose into d-glucose. In a similar way it can be shown also for other ferments that the fermentability of a substance depends upon its chemical configuration.

III.

But this knowledge does not offer us much assistance in deciding the question whether it is a vital process of the yeast cell which makes fermentation possible, or whether the ferment of the yeast can exist independently of the life of the cell. Thirty years ago there was a lively controversy on this subject between Pasteur and Liebig. For Pasteur the process of fermentation was a phenomenon accompanying the life phenomenon of yeast. "Fermentation begins and ends with the life of yeast. Alcoholic fermentation never takes place without simultaneous organisation, development, and reproduction, i. e., without continuance of life." Liebig, however, attacked this vitalistic conception of Pasteur. To him life phenomena were only phenomena of motion and he did not accept Pasteur's explanation when he said that fermentation was a physiological process. Liebig himself considered that an explanation of the process of fermentation was only possible by means of physics and chemistry. Liebig compared the effect produced by the ferment to that produced by heat upon organic molecules. In both cases the motion affects the internal arrangement of molecules. He mentioned that acetic acid is split up into carbonic acid and aceton by heat, similarly as sugar is split up by yeast into carbon dioxide and alcohol. But there was still another and stronger argument in favor of Liebig's view. It had been shown previously that certain ferments originally contained in living cells can be separated from the living cell and yet continue to produce the same fermentative effects. For instance, living yeast is able to decompose salicine into saligenine and an acid, yet it was shown that a soluble substance emulsine is able to produce the same fermentation. Liebig argues from this as follows: "If we ascribe the decomposition of salicine by yeast to a physiological process, namely, the growth and development of the yeast, as Pasteur has done, we are not able to explain the effect of the emulsine. In addition, both the yeast and the emulsine have one peculiarity in common. If heated in water to the boiling point of the latter, they lose their fermentative power. Hence it is more probable that the yeast cell and emulsine owe their fermentative effect upon salicine to the same chemical compounds or conditions." . . . "We can imagine that the physiological process bears no other relation to the process of fermentation than to produce that substance which brings about the falling apart of the sugar and other organic compounds. Thus the physiological process would be necessary to produce this substance (ferment), but otherwise the life phenomena of the yeast would have no connexion with the process of fermentation."

Pasteur could not deny that the case of emulsine was contradictory to his vitalistic conception of fermentation. Neither could he deny it in the case of invertine, a soluble substance which can be extracted from the yeast with water and which afterwards continues to produce certain fermentative effects. But he saved his vitalistic views by adopting a discrimination proposed by Dumas, namely that there are two kinds of ferments: (*a*) soluble ferments like invertine, emulsine and diastase, which were called enzymes, and (*b*) living ferments that reproduce themselves like the yeast cell. The alcoholic fermentation of sugar was, according to the opinion of Pasteur, a process that could only be accomplished by the living yeast cell and hence differed fundamentally from the case of soluble ferments or enzymes.

IV.

During the following thirty years most authors accepted Pasteur's idea. The wonderful results of his bacteriological researches made the critics blind in regard to the weakness of his theory of fermentation. Only a few authors like Hoppe-Seyler stuck to the firm logic of Liebig. "The effect of a ferment on other substances," says Hoppe-Seyler, "only depends upon its chemical structure. If one says a ferment is an organism this statement cannot well have any other meaning except that we do not wish to discriminate between the whole organism and its constituents. The notion of an organised ferment that Pasteur and his followers applied to yeast can be applied with the same right to any living being and even to man."

Recently the controversy between Liebig and Pasteur has been decided in favor of Liebig. First of all, Emil Fischer tried to answer the question whether from a chemical point of view there was such a fundamental difference between organised ferments and soluble enzymes as Pasteur had assumed. We have seen that, in regard to the organised ferments, the stereochemical configuration of the molecule decides its fermentability. Fischer showed that exactly the same is true for enzymes like invertine and emulsine. He subjected two stereoisomeric compounds, α-methylglucoside and β-methylglucoside, to the effect of both enzymes. He found that invertine is able to split α-methylglucoside into methylalcohol and grape sugar, while it has no influence upon β-methylglucoside. Emulsine, however, splits β-methylglucoside into methylalcohol and grape sugar while it has no influence upon α-methylglucoside. Thus it was proved that in chemical regard there is no principal difference between ferment and enzyme.

In connexion with these researches Fischer intimated how it can happen that a ferment breaks up one compound while it cannot affect its stereoisomeric compound. Suppose the case of invertine which is able to ferment α-methylglucoside while it cannot affect β-methylglucoside. Both glucosides have dissymmetrical molecules. Fischer assumes that the enzymes too have a dissymmetry in their molecular configuration. "Their limited effect upon glucosides therefore might be explained by the assumption that the molecules can approach each other as closely as is required to bring about the chemical process only in the case of geometrically similar configuration. Metaphorically one can say that enzyme and glucoside must fit like lock and key in order to have a chemical effect upon each other.

The fact that the activity of enzymes is limited to such a high degree by the molecular geometry might be of some use for physiological research. But still more important seems to me the proof that the discrimination, heretofore accepted, between the chemical activity of the living cell and the activity of purely chemical compounds does not exist as far as molecular dissymmetry is concerned. By means of this proof the analogy between living and not-living ferments which Berzelius and Liebig emphasised so often is re-established in an essential point. (Fischer).

But the opponents of Liebig still could claim that the alcoholic fermentation of grape sugar could only be accomplished by living yeast and that no adherent of Liebig had succeeded in extracting an enzyme from the living cell which could bring about the alcoholic fermentation of sugar. Until this could be done Pasteur's view was justifiable, namely, that the alcoholic fermentation of sugar is a life phenomenon of the yeast and that there is a fundamental difference between living ferments and enzymes.

Very recently, however, this objection too has been done away with. Buchner has succeeded in extracting an enzyme from the yeast which transforms sugar into alcohol and carbonic acid. He has thus brought about this kind of fermentation without living yeast. Hence the correctness of Liebig's theory was entirely confirmed. The reason which prevented the isolation of the enzyme of alcoholic fermentation from the yeast so much longer than the isolation of the invertine was a purely technical one. It requires a high pressure in order to separate the enzyme of alcoholic fermentation from the yeast.

Thus it is proved that the means which the living body possesses of transforming dead matter into living matter are enzymes which can exist independently and outside of living matter.

V.

The decomposition of large molecules into smaller building stones by enzymes is only one act of assimilation. The second act is the building up of new and different molecules from these building stones. The old belief was that such a synthesis was only possible in plant cells, but this is wrong. We know of a series of synthetical processes in animal cells, for instance the formation of hippuric acid from benzoic acid and glycocoll in the cells of the kidney. While fermentations can take place without oxygen, oxygen is absolutely necessary for this synthesis. Synthetical processes are just as general and essential for the life of animals as for the life of plants.

That the synthetical side of assimilation depends upon the fermentative side of it can be proved directly. In our body carbohydrates are stored in the form of animal starch. The molecule of glycogen is much larger than that of sugar and evidently originates through a process of condensation from the latter. Voit was the first to assume and Cremer has proved that only such sugars are good builders of glycogen which are easily fermentable with yeast. The yeast cells resemble the human cells in that they are able to store their carbohydrates in the form of glycogen and not in the form of starch as the green plant cells do. This discovery was made by Errera. Hence our cells as well as those of the yeast are able to form products of condensation only from those sugars whose configuration makes them an easy prey to the enzymes of the yeast cell or of our body.

At present we have no data concerning the molecular configuration and the fermentation of proteid molecules but there is no reason to assume that the principles which hold good for the assimilation of the carbohydrates should not hold good for the assimilation of proteid molecules. All the facts which at present allow us to draw a conclusion upon the assimilation of the proteids point out that both groups of bodies behave similarly as far as assimilation is concerned.

In the process of assimilation the geometrical configuration of the molecules may play still another rôle. It might be possible that the form of the molecules present in the living matter predetermines the form of the molecule into which the smaller building stones are put together in the synthetical phase of assimilation.

VI.

From what we have said it is clear that the first step toward the artificial production of matter which is able to assimilate depends upon our further knowledge of the nature of enzymes. This knowledge must be preceded by an understanding of the configuration of the proteid molecules. It is certain that the analysis of the enzymes is a problem which belongs to the realm of pure or physical chemistry. There is no reason to doubt that as soon as an analysis of the enzymes has been accomplished their synthesis will be accomplished too. Of course we are not yet able to judge how great the technical difficulties will be.

But the data which already exist suffice to allow the understanding of one essential point in the problem of heredity, namely how it happens that from the germ of an animal only an animal of the same species and of no other species can develop. The cause for this is that the germ of each species is only able to produce synthetically the typical compounds characteristic of this species. But as the assimilation through the germ of an animal is determined by the nature of the enzymes it contains, we must form the conclusion that the egg or the sexual cells are in so far bearers of heredity as they are the bearers or producers of specific enzymes which are characteristic for each species.

The problem of assimilation is at the same time the fundamental problem of heredity. Any theory of heredity must be based upon the mechanics of assimilation. We therefore have to substitute for or add to our purely morphological hypotheses of heredity a chemical theory. We do not need to be surprised at this. Living organisms are in the first place chemical machines and the process of embryonic development is determined by a definite series of chemical changes. It can be shown indeed that for the heredity of instincts as well as that of forms we do not need to assume anything more complicated in the sexual cells than the presence of specific chemical compounds especially enzymes or zymogens.[1] They are the true bearers of heredity.

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[1] Cf. the article "On Egg Structure and the Heredity Instincts." *The Monist.* July, 1897